SCIENCE CAPSULES

A Large-Scale Analysis of Gene Expression in Ovarian Cancer Suggests Novel Pathways and Reveals Novel Markers for this Disease. Ovarian cancer is the fifth most common cause of cancer death among women in the U.S., yet it is very poorly understood. Ovarian cancer affects older women disproportionately. Because there are few early symptoms, and no sensitive screening tests for use in the general population, it is typically diagnosed in late stages, when treatment is difficult and usually unsuccessful. More detailed knowledge of gene expression in ovarian cancer is crucial to a better understanding of how ovarian tumors form and to identifying novel targets for diagnosis and therapy. Serial Analysis of Gene Expression (SAGE) is a powerful method for analyzing the genes expressed in any cell or tissue. Researchers developed SAGE libraries representing the genes expressed in various normal and cancerous ovarian tissues and identified many genes that were expressed differently in normal ovary and in ovarian cancer cells. The genes identified by this method have the potential to become useful targets for early detection and therapy. In addition, this work provides a framework for a detailed understanding of how ovarian tumors form at the molecular level.

Hough CD, Sherman-Baust CA, Pizer ES, Montz FJ, Im DD, Rosenshein NB, Cho KR, Riggins GJ, and Morin PJ: Large-scale serial analysis of gene expression reveals genes differentially expressed in ovarian cancer. Cancer Research 60: 6281-6287, 2000.

Hough CD, Cho KR, Schwartz DS, Zonderman AB, and Morin PJ: Coordinately up-regulated genes in ovarian cancer. Cancer Research 61: 3869-3876, 2001.

Racial Differences in Cognitive Performance in Elders Disappear when Quality of Education is Assessed. Racial comparisons on intelligence tests, neuropsychological tests, cognitive tests, and dementia batteries generally have shown that despite equating the groups on variables such as years of education and socioeconomic status, African-Americans score lower on these measures than Caucasians. In this study, investigators reassessed the results of a standard neuropsychological test battery using an estimate of quality of education – the individual's score on the Reading Recognition subtest from the Wide Range Achievement Test (WRAT). After adjusting for reading score on the WRAT, the majority of previously noted test score differences between African-Americans and Caucasians became non-significant. This approach not only identifies factors which can account for ethnic group differences on cognitive tests but also can be used in the development of new cognitive tests and measures that are culturally fair.

Manly JJ, Jacobs DM, Touradji P, Small SA and Stern Y: Reading level attenuates differences in neuropsychological test performance between African American and White elders. Journal of the International Neuropsychological Society. (in press).

MAD2 Gene Linked to Genomic Instability in Aggressive, Drug Resistant Tumors. NIH-supported research has found that expression of a protein (MAD2), which monitors one of the

checkpoints in normal cell division, is directly linked to genomic instability and human cancers. These results have implications for cancer diagnosis and treatment. A number of cancers including breast, colon, and lung cancer, exhibit genomic instability, the hallmark of most aggressive cancers. The relationship between MAD2 expression and genomic instability helps explain the resistance of some tumors to cancer-fighting drugs and may make it possible to predict a tumor's aggressiveness more accurately.

Michel LS, Liberal V, Chatterjee A, Kirchwegger R, Pasche B, Gerald W, Dobles M, Sorger PK, Murty VVVS, and Benezra R: MAD2 haplo-insufficiency causes premature anaphase and chromosome instability in mammalian cells. Nature 409: 355-359, 2001.

Familial Mania Predicts Switch from Childhood Depression to Adolescent Bipolar Disorder. Prepubertal depressed children who participated in a pharmacologic treatment study at age 10 (not including children with attention deficit hyperactivity disorder) were reassessed as adults 10 years later. At the adult follow-up assessment, nearly half were diagnosed with a bipolar disorder. Of those diagnosed, one-third had Bipolar I (the more severe form of the disorder). Family history data, obtained at follow-up from the participants' mothers, revealed that parental and grandparental mania was predictive of Bipolar I disorder. This finding suggests that clinicians should collect family history data when prepubertal children are diagnosed with depression. In addition, depressed children with a family history of affective disorders should be monitored especially for signs of mania and be offered immediate treatment should they switch to bipolar disorder.

Geller B, Zimerman B, Williams M, Bolhofner K, and Craney JL: Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. American Journal of Psychiatry 158: 125-127, 2001.

Schizophrenia May Not Cause Long-term Cognitive Decline. Hallucinations, delusions, and disordered thinking are hallmarks of schizophrenia. In past years, researchers have focused on understanding the cognitive symptoms that accompany schizophrenia; more recently, however, there have been reports suggesting that schizophrenia itself causes long-term cognitive decline, and these have been used as arguments for earlier intervention and sustained treatment. In this study, investigators followed a sample of 142 individuals with schizophrenia over an average of three years and given a comprehensive battery of cognitive tests. Although the persons with schizophrenia performed worse than healthy adults, there was no evidence that they showed progressive worsening in cognitive symptoms. Overall, the cognitive symptoms of schizophrenia appear to be stable.

Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, and Jeste DV: Stability and course of neuropsychological deficits in schizophrenia. Archives of General Psychiatry 58: 24-32, 2001.

Gene for Myotonic Dystrophy Type 2. Myotonic dystrophy, the most common adult form of muscular dystrophy, causes a characteristic pattern of muscle loss, problems with relaxing

muscles (myotonia), and effects on the heart, eyes and hormones. In 1992, scientists discovered the gene defect that causes one subtype of myotonic dystrophy (DM1), although exactly how this mutation produces the complex symptoms of the disease is still not clear. Now, researchers have determined what causes the second form of myotonic dystrophy (DM2). The defect is in a different gene, one for a "zinc finger protein" called ZNF9. The finding should allow development of a genetic diagnostic test. The result also provides important clues to the causes of myotonic dystrophy. In both DM1 and DM2 the gene defect is a particular type of mutation, called an expansion, not in the blueprint for the protein itself, but in part of the gene that influences how the DNA of the gene is read out to form RNA, which in turn guides the formation of proteins.

Liquori CL, Ricker K, Moseley ML, Jacobsen JF, Kress W, Naylor SL, Day JW and Ranum LPW: Myotonic dystrophy type 2 causes by CCTG expansion in intron 1 of ZNF9. Science 293: 864-867, 2001.

Imaging Stroke Recovery. Many people experience difficulties with speech and language following a stroke, especially if the left side of the brain is affected. Why some stroke patients recover language quite well, and others not, is poorly understood. Scientists have now begun to explore the mechanisms of recovery by using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to monitor brain activity as patients perform language tasks during the period of recovery from stroke. Right brain structures corresponding to the areas in the damaged left brain appear to take on new language functions in some patients. However, recovery appears to be better when parts of the left language area resume their former role. These are just the early results in a continuing effort to clarify how the brain recovers, identify factors that predict recovery, and provide guidance to improve rehabilitation techniques.

Rosen HJ, Petersen SE, Linenweber MR, Snyder AZ, White DA, Chapman L, Dromerick AW, Fiez JA, and Corbetta M: Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 55: 1883-1892, 2000.

Some Adolescent Smokers May Be Self-medicating. Understanding why children begin to smoke may be key in developing effective prevention and treatment approaches. A recent study of adolescent smokers in a treatment program assessed inattention and hyperactivity symptoms and their relationship to smoking behaviors. The researchers found that adolescent smokers with frequent symptoms of inattention were using nicotine as a stimulant drug to help manage their symptoms.

Lerman C, Audrain J, Tercyak K, Hawk, LWJr, Bush A, Crystal-Mansour S, Rose C, Niaur R, and Epstein LH: Attention-Deficit Hyperactivity Disorder (ADHD) symptoms and smoking patterns among participants in a smoking cessation program. Nicotine and Tobacco Research (in press 2001).

Measuring Progression of Alzheimer's Disease. Hallmark features of Alzheimer's disease include progressive and substantial loss of cerebral gray matter together with decline in neuronal

and cognitive functioning. A major clinical challenge is the objective, noninvasive tracking of biochemical markers of neuronal and functional deterioration. In a recent study, researchers used proton magnetic resonance spectroscopic imaging (MRSI) and structural magnetic resonance imaging (MRI) to measure concentrations of the chemical N-acetyl aspartate (NAA), which is a marker for living neurons, in a group of Alzheimer patients. NAA concentrations decreased during the course of one year as Alzheimer's disease progressed from mild to moderate. Thus, NAA gray-matter concentration is a suitable measure for the detection and monitoring of deterioration or neuronal integrity with Alzheimer's disease progression and possibly of improvement in neuronal function with treatment.

Adalsteinsson E, Sullivan EV, Kleinhans N, Spielman DM, and Pfefferbaum A: Longitudinal decline of the neuronal marker N-acetyl aspartate in Alzheimer's Disease. Lancet 355: 1696-1697, 2000.

Screening for Hemochromatosis. Hemochromatosis, a treatable disorder involving iron deposition in tissues, occurs in people carrying mutations, or changes, in both copies of the hemochromatosis gene (HFE). In this study, relatives of people with hemochromatosis were tested, and those relatives who had mutations in both copies of their HFE gene were further evaluated. The researchers reported that in these clinically unselected relatives disease-related conditions (especially affecting the liver or joints) were found in 52 percent of men over 40 years of age and 16 percent of women over 50 years of age. These data emphasize the importance of screening relatives of persons with hemochromatosis.

Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, Edwards CQ, and Kushner JP: Disease-related conditions in relatives of patients with hemochromatosis. The New England Journal of Medicine 343: 1529-1535, 2000.

Characterization of the Autism Gene. Autism is a neurodevelopmental disorder that usually arises because of a complex genetic predisposition. The International Molecular Genetic Study of Autism Consortium, with participation by pediatricians at the Yale University General Clinical Research Center, completed linkage analyses of 170 families. Evaluation of 125 sibling pairs revealed two regions on chromosome 7q associated with autistic disorders. Identification of specific mutations within the human genome will enable early detection and intervention and, perhaps, provide a rationale for therapeutic correction of various genetic diseases.

International Molecular Genetic Study of Autism Consortium (IMGSAC): Further characterization of the autism susceptibility locus *AUTS1* on chromosome 7q. Human Molecular Genetics 10: 973-982, 2001.

Ductal Lavage and Methylation-Specific PCR for Breast Cancer Diagnosis. Most breast cancers originate in the epithelial cells that line the ductal/lobular units of the breast milk ducts. Nipple aspiration, the traditional method of collecting ductal epithelial cells for diagnosis of abnormalities, generally yields few epithelial cells and may collect cells from only some portions of the milk ducts. Ductal lavage (DL), a newly developed method of epithelial cell collection

using a microcatheter that is introduced into the nipple duct openings, recovers far greater numbers of ductal epithelial cells than is possible by nipple aspiration alone. DL is safe, well-tolerated, and minimally invasive, and may be a useful adjunct to mammography and other currently available imaging modalities for the early detection of abnormal breast lesions.

Evron E, Dooley WC, Umbricht CB, Rosenthal D, Sacchi N, Gabrielson E, So AB, Hung DT, Ljung B, Davidson NE, and Sukumar S: Detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR. Lancet 357: 1335-1336, 2001.

A Possible Marker for Invasive Breast Cancer. Researchers have identified a mutant estrogen receptor α (Erα) whose presence in precancerous breast lesions may indicate increased risk of progression to invasive breast cancer. In a recent study, the mutation was found in 62 percent of invasive breast tumors, but was not present in noncancerous breast lesions (such as fibroadenoma of the breast); it was also significantly more common in cancers that had spread to the lymph nodes than in cancers that remained localized to the breast. This is the earliest and most frequent mutation yet detected in precancerous breast lesions and invasive breast cancers, and may help doctors determine which women with precancerous breast conditions are at highest risk for invasive cancer and would most benefit from aggressive treatment.

Fuqua SAW, Wiltschke C, Zhang QX, Borg Å., Castles CG, Friedrichs WE, Hopp T, Hilsenbeck S, Mohsin S, O'Connell P, and Allred DC: A hypersensitive estrogen receptor a mutation in premalignant breast hyperplasias. Cancer Research, 60: 4026-4029, 2000.

Invasion-specific Markers for Pancreatic Cancer. Invasion-specific markers are substances (such as proteins) that are produced by an invasive tumor or the body's reaction to the tumor; such markers might not be present in normal tissues at a high level. Researchers have identified dozens of invasion-specific markers of pancreatic cancer. Many of these are new markers not previously considered as cancer markers, and some are known to be secreted and to be detectable in simple blood samples. Efforts are underway to evaluate these candidates and develop the most reliable ones for use in assays for cancer, to aid medical imaging, and to serve as targets for the development of invasion-specific anticancer therapy.

Ryu B, Jones J, Hollingsworth MA, Hruban RH, and Kern SE: Invasion-specific genes in malignancy: Serial analysis of gene expression comparisons of primary and passaged cancers. Cancer Research 61: 1833-1838, 2001.

Argani P, Rosty C, Reiter RE, Wilentz RE, Murugesan S, Leach SB, Ryu B, Goggins M, Yeo CJ, Cameron JL, Kern SE, and Hruban RH: Discovery of new markers of cancer through serial analysis of gene expression (SAGE): prostate stem cell antigen (PSCA) is overexpressed in pancreatic adenocarcinoma. Cancer Research 61: 4320-4324, 2001.

Device May Enable Detection of Lung Cancer From Chest X-Rays. Only 15 percent of lung cancers are identified at an early, treatable stage. A new technology may make it possible to detect lung cancer from a chest x-ray, enabling the early detection of many more tumors. The

device digitizes chest x-rays and marks any suspicious nodules for review by a radiologist. In a recent clinical trial, the system improved radiologists' detection of small lung cancers by about 20 percent.

Freedman M, Lo SC B, Lure F, Xe XW, Lin J, Zhao H, Osicka T, and Zhang R: Computer aided detection of lung cancer on chest radiographs. Algorithm Performance vs Radiologists' Performance by Size of Cancer, to be published in Medical Imaging 2001: Image Perception and Performance Proceedings. Eds: Elizabeth A. Krupinski, Health Sciences Ctr./Univ. of Arizona; Dev P. Chakraborty, Univ. of Pennsylvania, ISBN 0-8194-4010-8, June 2001.

Freedman M, Osicka T, Lo S-C B, Lure F, Xu X-W, Lin J, and Zhang R: Methods for Identifying Changes in Radiologists' Behavioral Operating Point of Sensitivity-Specificity Trade-Offs within an ROC Study of the Use of Computer Aided Detection of Lung Cancer, to be published in Medical Imaging 2001: Visualization, Display, and Image-Guided Procedures Proceedings. Ed: Seong Ki Mun, Georgetown Univ. Medical Ctr. ISBN 0-8194-4005-1, May 2001.

Detection of Cancer-Predisposing Mutations in Mitochondrial DNA. Most efforts to detect genetic alterations that predispose an individual to cancer have targeted DNA in the cell's nucleus. However, DNA is also present in the mitochondria, the cell's principal energy source, and researchers have found that mutations in mitochondrial DNA are more easily detected than those in nuclear DNA. In addition, recent studies in pancreatic cancer have found that the cancer cells harbored six to eight times more mitochondrial DNA than normal cells, but that their nuclear DNA was not comparably increased. This newly identified property would provide a considerable advantage for detection systems that would detect mitochondrial instead of DNA mutations, and validates the need for investment in technology dedicated to analysis of mitochondrial DNA, such as a "mitochip" technology.

Jones JB, Song JJ, Hempen PM, Parmigiani G, Hruban RH, and Kern SE: Detection of mitochondrial DNA mutations in pancreatic cancer offers a "mass"-ive advantage over detection of nuclear DNA mutations. Cancer Research. 61: 1299-1304, 2001.

Development of a Simple and Reliable HIV Test for Resource Poor Settings. Approximately one third of infants born to HIV-1 infected mothers become infected with HIV-1. Rapid and accurate diagnoses are important so that these newborns receive appropriate care. However, diagnosis in countries with limited resources is hampered by the collection and storage requirements of current tests. NIH-supported researchers collected blood on filter paper from HIV-infected and uninfected adults and children in the U.S. and in Peru. The filter papers were then assessed for content of a specific HIV gene using standard technologies that do not require elaborate processing of the papers. This simple approach permits HIV-1 diagnosis in infants and is close to 100 percent accurate without requiring special training and materials. It is effective even if the blood specimen is stored for long periods of time in warm climates. These features make the test ideal for diagnosing HIV-1 in infants worldwide, especially in developing countries where refrigeration, sophisticated equipment, and health care personnel are limited.

Beck IA, Drennan KD, Melvin AJ, Mohan KM, Herz AM, Alarcón J, Piscoya J, Velázquez C, and Frenkel LM: Simple, sensitive and specific detection of human immunodeficiency virus type 1 subtype B DNA in dried blood samples in diagnosis in infants in the field. Journal of Clinical Microbiology 39: 29-33, 2001.

Prenatal Stress and Outlook Affects Birth Outcomes in High-Risk Pregnancies. Nurse researchers studied the effects of chronic stress in pregnancy. A group of high-risk pregnant women completed a series of questionnaires to assess perceived stress, anxiety level, pregnancy-specific distress, health behaviors, and disposition. Pessimistic women experienced more stress during their pregnancy and delivered infants of lower birth weight. Optimistic women reported more regular exercise and other health behaviors linked to more positive birth outcomes. Maternal disposition may affect birth outcomes and fetal health as much as ethnicity or medical risk.

Lobel M, DeVincent CJ, Kaminer A, and Meyer BA: The impact of prenatal maternal stress and optimistic disposition on birth outcomes in medically high-risk women. Health Psychology 19: 544-553, 2000.

Genetic Analysis of Digestive Physiology Using Fluorescent Lipids. Zebrafish are a useful model for studying fat metabolism in mammals. Their larvae process fats in the intestine and liver and respond to cholesterol-blocking drugs in a manner similar to humans. Scientists recently assayed fat metabolism in living larvae by modifying fluorescently tagged lipids with the aim of identifying genes relevant to human lipid metabolism and disease. Genetic screening identified zebrafish mutants, such as *fat free* that show normal digestive organ form and structure but reduced lipid and cholesterol processing. These findings predict that genetic screens can identify genes involved in diseases of lipid metabolism, including atherosclerosis (narrowing of the arteries), as well as in disorders of biliary secretion, such as biliary atresia, and forms of cancer, in which lipid signaling plays an important role.

Farber SA, Pack M, Ho SY, Johnson ID, Wagner DS, Dosch R, Mullins MC, Hendrickson HS, Hendrickson EK, and Halpern ME: Genetic analysis of digestive physiology using fluorescent phospholipid reporters. Science 292: 1385-1388, 2001.

Bladder Cancer Diagnosed by Simple Urine Test. Researchers have developed a urine test that identifies a protein found in bladder cancer cells. The test could lead to an easier, less invasive way to detect the disease. Right now, there is no simple approved test for bladder cancer. The simple, noninvasive test described in the current report screens for a protein called survivin, which is undetectable in most normal adult tissues, but is prominently expressed in common human cancers. Survivin is an inhibitor of programmed, or "natural," cell death. When the survivin gene is switched on, subsequent production of survivin allows mutated cells to survive. Switching off the survivin gene stops the progression of cancer. The new test uses an antibody to detect survivin in urine samples. In a series of experiments, survivin was found in all (46) urine samples of patients with new or recurrent bladder cancer, but not in the urine of any of the healthy volunteers (17) or patients with other urologic cancers, i.e. kidney, prostate,

cervical, or vaginal cancer (30). In addition, of 60 patients with known bladder disease other than cancer, three did test positively for survivin. After testing these patients with the standard invasive test, researchers found one to have cancer, diagnosed another patient with cancer six months after the test, and are still monitoring the third patient for possible cancer. These results indicate that the sensitivity of the urine survivin test for new or recurrent bladder cancer was 100 per cent, and its specificity for other noncancerous and benign genitourinary tract disease was 95 per cent. The researchers suggest that their simple, noninvasive, urine survivin antibody test would be a useful complement to other diagnostic markers to monitor bladder cancer patients more effectively, and to identify early recurrences and new bladder cancers. Indeed, this test appears to be far superior to existing tests for bladder cancer in terms of sensitivity, specificity, ease of use, point-of-service suitability, and cost-effectiveness. With this advance, it is hoped that a urine test for bladder cancer could become as routine as other regular check-ups, such as prostate specific antigen (PSA) tests for prostate cancer.

Smith SD, Wheeler MA, Plescia J, Colberg JW, Weiss RM, and Altieri DC: Urine detection of survivin and diagnosis of bladder cancer. Journal of the American Medical Association 285: 324-328, 2001.

A New Way to Monitor Progression of Polycystic Kidney Disease. Polycystic Kidney Disease (PKD) is an inherited kidney disease characterized by progressive kidney enlargement and reduced kidney function. Kidney function is compromised by growth of fluid-filled cysts that can gradually "squeeze out" the normal kidney tissue. Until recently, doctors have had no rigorous guidelines for judging whether or not a PKD patient is likely to develop kidney failure and how quickly the disease may progress. A study has now confirmed doctors' anecdotal observations that kidney enlargement due to increased number and size of cysts is an accurate marker of PKD progression to kidney failure. The study used computed tomography (CT) scans to visualize kidney size and monitor the number of kidney cysts over the course of several years. The rate of kidney enlargement varied widely from patient to patient, but it was directly linked to the number or size of kidney cysts. Patients whose kidneys became enlarged were more likely to develop kidney failure, and those whose kidneys remained small were more likely to maintain relatively normal kidney function. This study validated the use of CT scanning as a method for monitoring progression of PKD. Use of CT scanning will also enable doctors to judge how well potential treatments work by documenting whether kidneys and cysts grow, shrink, or remain the same in size.

Sise C, Kusaka M, Wetzel LH, Winklhofer F, Cowley BD, Cook LT, Gordon M, and Grantham JJ: Volumetric determination of progression in autosomal dominant polycystic kidney disease by computed tomography. Kidney International 58: 2492-2501, 2000.